CASE TN1A CIP

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

ULLAH ET AL.

APPLICATION NO: 09/848,448

FILED: May 3, 2001

FOR: HIGH DRUG LOAD ACID LABILE PHARMACEUTICAL COMPOSITION

Art Unit: 1615

Examiner: Susan T. Tran

15/2/Appeal Brief (3)

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P.O. Box 1450
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Bet 10-14-03

APPEAL BRIEF

Sir:

This is an appeal from the Final Office Action mailed January 24, 2003 where Claims 1, 4 to 24 and 27 to 31 of the above-identified application are finally rejected.

(1) REAL PARTY IN INTEREST

The real party in interest in this appeal is Bristol-Myers Squibb Company, a Delaware corporation, having a place of business at Lawrenceville-Princeton Road, Princeton, NJ 08543-4000. Bristol-Myers Squibb Company is the assignee and owner of the entire interest in the above-identified application by virtue of an assignment filed in application Serial No. 09/083,597, now abandoned, and a parent of the subject application, and which was recorded in the United States Patent and Trademark Office on November 25, 1998 at Reel/Frame 9606/0024 (copy of the Notice of Recordation of Assignment being enclosed herewith).

(2) RELATED APPEALS AND INTERFERENCES

The undersigned knows of no other appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) STATUS OF CLAIMS

Claims 1, 4 to 24 and 27 to 31 have been finally rejected and Claims 1, 4 and 6 have been cancelled via the attached "Supplemental Amendment After Final Rejection" filed herewith. Thus, Claims 5, 7 to 24 and 27 to 31 remain under appeal.

(4) STATUS OF AMENDMENTS

As indicated, the claims have been amended after final rejection in a Supplemental Amendment After Final Rejection filed herewith.

Claims 1 and 4 have been cancelled and the subject matter of Claim 6 has been incorporated into Claim 5 to reduce the issues on appeal.

The attached "Claims on Appeal" reflect the above-described amendments.

(5) SUMMARY OF INVENTION

Appellants' invention as claimed is directed to an oral dosage ddI formulation which is in the form of an enteric coated beadlet which includes a high concentration of 2',3'-dideoxyinosine (ddI) in the core, namely from about 80 to about 100% by weight ddI. The formulation may also include a disintegrant and a binder.

Claim 5 specifically defines a pharmaceutical composition containing a core in the form of a beadlet and an enteric coating therefor, the core containing from about 80 to about 100% by weight ddI, an optional disintegrant and optional binder, the composition being devoid of a protective coat or subcoat between the core and the enteric coating. The protective coat or subcoat is unnecessary because the ddI will not cause the enteric coating to dissolve prematurely.

Claim 7 depends from Claim 5 and defines a weight ratio of enteric coating to core of between 0.05:1 to about 0.6:1.

Claims 8 to 15 depend from Claim 5 directly and indirectly and define aspects of the enteric coating.

Claims 16 to 20 depend directly and indirectly from Claim 5 and define aspects of an anti-adherent disposed on the enteric coating.

Claims 21 to 24 depend directly or indirectly from Claim 5 and define disintegrants or binders.

Claim 27 depends from Claim 5 and defines a specific core composition containing 95% by weight ddI.

Claims 28 to 31 depend directly and indirectly from Claim 5 and define capsule compositions.

It is submitted that Appellants' composition as claimed is patentable over all cited references taken in any combination.

(6) ISSUE

Is Appellants' composition as defined in Claims 5, 7 to 24 and 27 to 31 unobvious from and therefore patentable over Morella et al. WO 94/03160 in view of Howard et al. U.S. Patent No. 5,049,394 and Bogardus et al. U.S. Patent No. 6,207,650?

Obviousness under 35 U.S.C. §103

A determination of obviousness under 35 U.S.C. §103 is a legal conclusion based upon factual evidence. The factual inquiries on which the conclusion is based are those defined in Graham v. John Deere Co., 383 U.S. 1 (1966), and restated in Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81 (Fed. Cir. 1986), cert. den. 107 S. Ct. 1606 (1987). These factual inquiries are:

(1) determining the scope and content of the prior art;

(2) ascertaining the differences between the invention and the prior art and the claims at issue, and

(3) resolving the level of ordinary skill in the pertinent art.

Obviousness is tested by what the combined teachings of the prior art references would have suggested to those of ordinary skill in the art, not by whether it might have been "obvious to try" a particular combination of elements from the prior art (In re Fine, 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988); In re Wiggins, 158 U.S.P.Q. 199 (1968); In re Mercier, 185 U.S.P.Q. 774 (1976); In re Antoine, 195 U.S.P.Q. 6 (1977); In re Goodwin, Margrave and Wagner, 198 U.S.P.Q. 1 (1978); In re Yates, 211 U.S.P.Q. 1149 (1981)). The teachings of the prior art can only be combined if there is some suggestion or incentive in the prior art to do so (ACS Hospital Systems, Inc. v. Montefiore Hosp. et al., 221 U.S.P.Q. 929 (CAFC 1984)).

Further, as stated in W.L. Gore & Assoc., Inc. v. Garlock, Inc., 220 U.S.P.Q. 303 (Fed. Cir. 1984):

> To imbue one of ordinary skill in the art with knowledge of the invention . . . , when no prior art reference or references . . . convey or suggest that knowledge, is to fall

victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher.

Applying the above law, it will be seen that Appellants' invention as claimed Claims 5, 7 to 24 and 27 to 31 is patentable over the cited references each taken alone or in combination.

(7) GROUPING OF CLAIMS

All of the rejected Claims 5, 7 to 24 and 27 to 31 (as now amended and under appeal) stand or fall together.

(8) ARGUMENT

It is submitted that Appellants' high potency 2',3'-dideoxyinosine beadlets as claimed in Claims 5, 7 to 24 and 27 to 31 is patentable over Morella et al. WO 94/03160 (hereinafter "Morella et al.") taken in view of Howard et al. U.S. Patent No. 5,049,394 (hereinafter "Howard et al.") and Bogardus et al. U.S. Patent No. 6,207,650 (hereinafter "Bogardus et al.").

All of the Claims are rejected under 35 U.S.C. §103(a) as being unpatentable over Morella et al., in view of Howard et al., and Bogardus et al. The Examiner contends in the Final Rejection as follows:

> "Morella teaches pelletized composition comprising core including 0.1 to 95% active ingredient, 0.1 to 55% binding agent, filler, carrier, excipients, and glidants (see abstract, and pages 6-7). The active ingredient can be erythromycin (page 4). The core is further being coated with 3 to 50% polymer, 0 to 50% plasticizer (pages 8-9, and formulations 1-7).
>
> "Howard teaches high drug load pharmaceutical composition comprising from about 80% to about 96% of drug, *e.g.,* erythromycin; from about 1 % to about 12% binder-plasticizer, such as, hydrophilic polymers; 0.5% to about 12% of starch-based excipient, such as, sodium starch glycolate, pregelatinized starch, or polyvinylpyrrolidone; and from about 0.2 to about 5% water-soluble binder, *e.g.,* hydroxypropylmethyl cellulose (columns 2-4). The composition is in spheronizer to form beads that may be coated with film former and plasticizer, and the coated beads can be filled into hard shell capsules (columns 4-5).
>
> "Howard and Morella are silent as to the teaching of 2',3'-dideoxyinosine as active agent.
>
> "Bogardus teaches pharmaceutical composition comprising antiviral drug, *e.g.,* 2',3'-dideoxyinosine in the form of powders, granules that can be enteric coated (columns 4-5). Accordingly, it would have been prima facie obvious for one of ordinary skill in the art to prepare the composition of Morella and Howard using 2',3'-dideoxyinosine as active ingredient in view of the teaching of Bogardus because the references teach the advantageous result of acid labile drug in oral dosage form."

It is submitted that Appellants' invention as claimed is patentable over Morella et al.

Morella et al. discloses a pelletized sustained release pharmaceutical composition which includes a core element which includes 0.1 to 95% by weight of an active ingredient having "low water solubility". By "low water solubility" is meant an aqueous solubility of about 1 in 1,000 to 10,000 (volume in mL) (see page 3, lines 15 to 18 of Morella et al.). Examples of active ingredient of low water solubility are disclosed at pages 3 and 4 includes a

> "...xanthine oxidase inhibitor, antiarrhythmic, anticoagulant, gold compound, dopamine agonist, diuretic, anticancer, skeletal muscle relaxant, antimalarial, hormone, antipsychotic, antihistamine, immunosuppressive, antileprosy, carbonic anhydrase inhibitor, antibiotic, antifungal, corticosteroid, MAO-1, vasodilator, thyroid agent, sympatholytic, H_2-antagonist, stimulant, anticoagulant, anticonvulsant, antituberculosis, hypoglycaemic, glucocorticoid or antidepressant agent.
>
> "The active ingredient of low aqueous solubility may be an NSAID or an acid or salt thereof. The NSAID ingredient in the pelletized sustained release pharmaceutical composition according to the present invention may be selected from low aqueous solubility forms of Diclofenac, Etodolac, Fenoprofen, Fluorbiprofen, Ibuprofen, Ibuproxan, Indomethacin, Ketoprofen, Ketorolac, Nabumetone, Naproxen, Phenylbutazone, Piroxicam, Priprofen, Tolmetin, Aspirin, Sulinac, Diflunisal, Indoprofen, Mefanamic Acid, Fenclozic Acid, Alclofenac, Bucloxic Acid, Meclofenamic Acid, Flufenamic Acid, Cinchophen Cinmetacin, Ibufenac, Furobufen, Prodolic Acid, Oxoproxin, Clonixin, Fluprofen, Flutiazin. The present invention is particularly applicable to NSAID's of low aqueous solubility. Diclofenac, Ketorolac and Indomethacin are preferred.
>
> "The active ingredient of low aqueous solubility may be any other suitable ingredient, for example low aqueous solubility forms of Allopurinal, Amiodarone Hydrochloride, Anisindione, Auranofin, Benzocaine, Bromocriptine Mesylate, Bumetanide, Busulfan, Chlorambucil, Chloroquine, Chlorphenesin Carbomate, Chloprothixene, Clemastine Fumarate, Dehydrocholic Acid, Dichlorphenamide, Doxycycline Monohydrate, Erythromycin, Etoposide, Griseofulvin, Haloperidol, Hydrocortisone, Levothyroxine Sodium, Liothyronine Sodium, Lovastatin, Mephenytoin, Methazolamide, Methclothiazide, Metyrosine, Nitrofarantoin, Norfloxacin, Oestropipate, Famotadine, Pemoline, Phenacemide, Pimozide, Quinethazone, Rifampin, Sulfisoxazole, Tamoxifen Citrate, Tetracycline, Tolazamide, Triamcinolone, Trichlormethiaside, Trimethoprim, Trimipramine Maleate, Uracil Mustard and acids or salts thereof."

Morella et al. sets out a listing of some 30 classes of drugs none of which includes AIDS drugs and sets out some 81 different drugs none of which includes ddI.

There is no disclosure or suggestion in Morella et al. of using 2',3'-dideoxyinosine (ddI) in their pellets. In fact, ddI has a water solubility at pH 6 of 27.3 mg/mL which is substantially higher than 1 mg/1000 mL or 1 mg/10,000 mL. Thus, ddI would not be considered an active ingredient of low water solubility and would not be included as a drug in Morella et al. Accordingly, it is clear that

Appellants' compositions as now claimed, which define the acid labile medicament as 2',3'-dideoxyinosine, are neither anticipated nor made obvious by Morella et al.

There is no disclosure or suggestion in Morella of a technique which would be applicable in making high concentration 2',3'-dideoxyinosine beadlets as claimed herein. One skilled in the art reading Morella et al. could not make Appellants' beadlets. Thus, Morella et al. is not a valid reference since its teaching would not enable one skilled in the art to make Appellants' beadlets as claimed. Furthermore, Morella et al. teaches a sustained release formulation. Appellants' formulation is not a sustained release formulation. Accordingly, it is clear that Appellants' beadlets are patentable over Morella et al.

It is submitted that Appellants' invention as claimed is patentable over Howard et al. As indicated, Appellants' composition as claimed defines the acid labile medicament as 2',3'-dideoxyinosine.

Howard et al. discloses beads containing more than about 80% by weight drug which drug may be an angiotensin converting enzyme (ACE) inhibitor, as well as

> "...anti-hypertensive agents such as nifedipine and verapamil, diuretics such as hydrochlorothiazide, bendroflumethiazide or chlorthalidone, beta-blockers such as propanolol HCl or atenolol and anti-infectives such as erythromycin, beta lactams, penicillins, other macrolides or lincosamides." (Col. 3, lines 23 to 28)

There is no disclosure or suggestion in Howard et al. of a pharmaceutical composition which includes 2',3'-dideoxyinosine as the pharmaceutical. There is no disclosure or suggestion in Howard et al. that the Howard et al. composition could be employed to carry 2',3'-dideoxyinosine. Furthermore, there is no disclosure or suggestion in Howard et al. of how to make beadlets containing 2',3'-dideoxyinosine containing at least 80% by weight ddI. There is no disclosure or suggestion of a procedure to enable one skilled in the art to prepare Appellants' beadlets. Accordingly, it is clear that Howard et al. does not anticipate or make obvious Appellants' composition as claimed.

As previously indicated, Morella et al. and Howard et al. disclose formulations which may be employed for various drugs none of which includes 2',3'-dideoxyinosine. These references do not disclose or suggest Appellants' inventive concept of a composition containing at least 80% by weight 2',3'-dideoxyinosine or a necessary procedure for making a composition containing such a high concentration of 2',3'-dideoxyinosine. Thus, even combining these references does not result in a teaching which would make Appellants' enteric coated ddI beadlets obvious to one skilled in the art.

Accordingly, it is submitted that Appellants' invention as claimed is patentable over each of Morella et al. and Howard et al. even when taken in combination.

U.S. Patent No. 6,207,650 to Bogardus et al. discloses salts of 2',3'-dideoxyinosine (not ddI, but salts of ddI) and pharmaceutical compositions containing salts of 2',3'-dideoxyinosine which include tablets, lozenges, capsules, powders, and granules, but not BEADLETS or PELLETS, which may contain from about 0.5 to 100% by weight of a salt of 2',3'-dideoxyinosine. Salts of ddI have a very basic pH of between 9.5-11. ddI has a pH of about 6 when dissolved in water. There is no disclosure or suggestion in Bogardus et al. of an enteric coated beadlet or pellet containing at least 80% by weight 2',3'-dideoxyinosine base compound which is the base compound and not a salt thereof. This is Appellants' inventive concept and it is neither disclosed nor suggested in Bogardus et al. Bogardus et al. has nothing to do whatsoever with pellets or beadlets or how to make pellets or beadlets containing large amounts of 2',3'-dideoxyinosine base compound and not a salt thereof.

Appellants' invention as claimed is defined as a pharmaceutical composition (Claim 5) which includes a core in the form of a beadlet which contains from about 80 to about 100% by weight of an acid labile medicament which is 2',3'-dideoxyinosine (ddI), and which core may also include a disintegrant and/or a binder, and an enteric coating for the core. Appellants specifically exclude the presence of a protective coat or subcoat between the core and the enteric coating since the enteric coating will not attack the ddI in the core and the ddI in the core will not attack or cause the enteric coating to dissolve or otherwise disintegrate prematurely. The enteric coating in Appellants' beadlets will dissolve at the desired time, that is, when it is subjected to a pH of 4.5 or higher. However, if the ddI in the core were to be replaced by a ddI salt as disclosed by Bogardus et al., and as suggested by the Examiner, the ddI salt which will be at a pH of 9.5 to 11 has a neutralizing capacity and could cause the enteric coating to prematurely dissolve (long before the beadlet reaches the intestines). As indicated in the Specification at page 87 starting on line 18, the enteric coating will permit drug release at a pH of 4.5 or higher (such as found in the upper intestines) and should not dissolve before it reaches the duodenum. If the enteric coat is in contact with the core containing the ddI salt of Bogardus et al., the enteric coat could dissolve upon storage even before it enters the body. Thus, if the Bogardus et al. ddI salt were to be used in the core the core would have to have a protective coat to prevent contact of the ddI salt with the enteric coat. Appellants' enteric coated beadlets as claimed specifically excludes a protective coat between the core and the enteric coating.

None of the cited references taken singly or in combination discloses or suggests or gives the slightest hint of a spheronized beadlet which contains 80 to 100% by weight of ddI or how to go about making such a spheronized beadlet containing at least 80% ddI.

Bogardus et al., the only reference cited which has anything to do with ddI, discloses highly water-soluble salts of ddI. As indicated in Column 5, starting at line 5, the salts have a "very high water solubility (>200 mg/ml), ideally suitable for high concentration, low volume IV-IM injectables." These salts have a "high alkalinity (pH 9.5-11)" which "allow for self-buffering against gastric acid. Thus, less buffer could be required in oral dosage forms."

ddI (not the salt form), on the other hand, is not as soluble in water as are the salts disclosed in Bogardus: compare water solubility of ddI: 27.3 mg/ml at pH 6 versus water solubility of the Na salt of ddI is >300 mg/mL at pH 9.5-11.

Since the Bogardus et al. salts of ddI are highly alkaline (pH 9.5-11), they do not require large amounts of buffers, whereas ddI (and not the salt thereof) is very acid labile (which degrades in the stomach when contacted with gastric acid) and requires large amounts of buffers or antacids which could lead to significant GI problems. In addition, use of large amounts of buffers with ddI requires large ddI tablets (a single dose is two tablets of 2.1 g each).

These problems are alleviated according to Appellants' invention by preparing smaller dosage forms, for example, beadlets containing high concentrations of ddI, which beadlets will include an enteric coating.

Until now, it has not been possible to formulate solid oral dosage forms containing large amounts of ddI (at least 80% by weight) without using large amounts of buffers or highly water soluble salt forms of ddI. Appellants are able to prepare beadlets containing at least 80% ddI by dusting the extrudate and the forming beadlet with the ddI.

As indicated in the Specification starting at page 7 line 18 "the enteric coating should provide for protection of the acid labile medicament at a pH less than 3 (such as found in the stomach) but will permit drug release at a pH of 4.5 or higher (such as found in the upper intestines)."

At page 7 of the Specification starting at line 31, it is indicated that "the enteric coating should begin to dissolve at a pH between about 4.5 and 5.5." Thus, it should be particularly noted that if the ddI salt were used in place of the ddI in the beadlets of the invention, the ddI salt which has an alkaline pH of 9.5 to 11 would cause the enteric coating to dissolve. Accordingly, to prevent dissolution of the enteric coating due to presence of the ddI salt in the core, you would have to employ a subcoat or protective coating between the core and the enteric coating. However, as indicated on page 9, starting at 17, the presence of a subcoat layer could delay drug release.

One way of getting around the problem of using the ddI salt in an enteric coated beadlet is to use acid to neutralize the ddI salt. If the ddI salt is neutralized, it will convert back to ddI. In such case, it is apparent that there would be no reason to use the ddI salt to begin with.

Bogardus et al. do not disclose or suggest spheronized beadlets of any kind, let alone spheronized beadlets containing ddI and at least 80% ddI at that. As indicated, if Appellants' beadlets were changed to include the ddI salt in place of ddI, Appellants' enteric coat would prematurely dissolve since the enteric coat dissolves at a pH of 4.5 or greater. This would destroy the integrity of the beadlets.

Although Bogardus et al. disclose pharmaceutical compositions containing 100 to 0.5% of the salt, Bogardus et al. do not disclose or suggest how to make a composition containing at least 80% by weight of the drug. Thus, Bogardus et al. do not teach one skilled in the art how to make a composition containing large amounts of ddI. The Bogardus disclosure does not teach or suggest how to make compositions containing at least 80% by weight ddI or even the ddI salt. Appellants' were only able to prepare their ddI beadlets containing at least 80% by weight ddI by the special procedure as described above in the working Examples.

The Examiner cites Bogardus et al. and states in the Advisory Action that "Bogardus is relied upon solely for the teaching of acid labile drug, such as 2',3'-dideoxyinosine," that is ddI. But Bogardus et al. do not disclose compositions containing ddI. ddI is an acid labile drug that degrades in stomach acids and therefore requires large amounts of buffers. Bogardus et al. disclose salts of ddI that are highly alkaline and thus are self-buffering, and do not require large amounts of buffers.

In view of the foregoing, it is clear that Appellants' enteric coated ddI beadlets as claimed is patentable over Bogardus et al.

It is also submitted that Appellants' enteric coated ddI beadlets as claimed is patentable over a combination of Morella et al., Howard et al. and Bogardus et al.

The combination of Morella et al., Howard et al. and Bogardus et al. does not disclose or suggest Appellants' spheronized beadlets containing at least 80% ddI or how to make them. Not one of the cited Morella et al., Howard et al. and Bogardus et al. references discloses or suggests how to make Appellants' high ddI concentration beadlets.

There is no disclosure or suggestion in any of the cited references each taken singly or in combination of forming beadlets containing at least 80% by weight 2',3'-dideoxyinosine or at least 80% by weight 2',3'-dideoxyinosine in the core. This is not easily accomplished and it is through use of a unique 2',3'-dideoxyinosine dusting step that such high concentrations are achievable as

described on page 12 of the Specification and in the working examples. As indicated on page 12, by dividing a dry blend of 2',3'-dideoxyinosine, binder and disintegrant into two portions, one portion of which is made into beadlets using a spheronizer, and the other portion of which is dusted onto the beadlets during spheronization, Appellants are able to make their beadlets having the desired high concentration of 2',3'-dideoxyinosine. The cited references are completely devoid of a teaching or suggestion as to how to make the enteric coated beadlets of the invention which contain at least 80% by weight.

The present situation with regard to lack of teaching in cited references of how to make the ddI beadlet formulation containing at least 80% by weight ddI is not unlike where the cited prior art names a compound but where no known or obvious method exists for making that compound and thus the cited prior art will not place the compound in the possession of the public. In re Hoeksena, 158 U.S.P.Q. 596 (CCPA 1968). A compound is not obvious if there is no known way or obvious way to prepare it. In re Hoeksema et al., supra. By the same token, a formulation is not obvious if there is no known way to prepare it. It is Appellants' contention that the cited prior art taken alone or in any combination does not disclose or suggest Appellants' enteric coated beadlet formulation as claimed or a method for preparing same or a method for preparing the Bogardus et al. formulation containing at least 80% by weight ddI salt, and therefore does not place Appellants' formulation in the public.

The Examiner has not established a prima facie case of obviousness. The cited references take in combination do not disclose or suggest a formulation containing at least 80% ddI. That this is apparent can be seen from the fact that none of the cited references even relates to ddI; Bogardus et al. only teaches salts of ddI which, as discussed above, would not be employed in a formulation as claimed herein. In addition, the cited references taken in combination do not teach how to make a ddI formulation containing at least 80% ddI. In determining patentability of a composition, it is appropriate to consider the manner of its preparation versus the prior art; if there is no disclosure of how to make it, it cannot be considered in the possession of the public. In re Hoeksema et al., supra. There is no disclosure in the cited art of how to make a formulation containing at least 80% ddI as explained hereinbefore.

In view of the above, it is clear that the Examiner has not cited any references which would make Appellants' formulation obvious.

It is also submitted that the very combination of Morella et al. taken in view of Howard et al. and Bogardus et al. is improper as lacking any foundation and could only be made with the use of

hindsight in view of Appellants' disclosure. The cited prior art does not provide a suggestion or basis for modifying Morella et al. and Howard et al. in view of Bogardus et al.

Morella et al. teach a pellet containing a low water solubility drug in an amount from 0.1 to 95%, and sets out a listing of some 30 classes of drugs none of which includes AIDS drugs and sets out some 81 different drugs none of which includes ddI.

Howard et al. discloses beads containing more than 80% by weight of an anti-hypertensive agent or anti-infective. There is no disclosure or suggestion of a formulation containing ddI.

Bogardus et al. discloses formulations containing 0.5 to 100% of a salt of ddI. There is no common thread which runs through the 3 cited references linking these references together.

The Examiner contends that it would be prima facie obvious to prepare the Morella or Howard compositions employing ddI as the active ingredient in view of Bogardus et al. But Morella relates to compositions containing a low water solubility drug. ddI and its salts are not low water solubility drugs. Accordingly, there would be no reason to combine Morella and Bogardus absent the use of hindsight in view of Appellants' disclosure.

Howard et al. relates to compositions containing anti-hypertensives and anti-infectives and has nothing whatsoever to do with anti-viral or AIDS drugs. Accordingly, there is no teaching or basis in Howard et al. or Bogardus et al. for combining these references absent the use of hindsight in view of Appellants' disclosure.

Finally, even if such a combination were made, Bogardus et al. does not teach compositions containing ddI but ddI salts which as discussed hereinbefore would not be the equivalent of ddI in formulations as claimed by Appellants. Thus, even if the combination of references were made, it still would not disclose or make obvious Appellants' beadlet formulation since none of the cited references teaches or suggests any composition containing ddI let alone enteric coated beadlets containing at least 80% ddI.

SUMMARY OF ARGUMENTS

Summing up, it is submitted that Appellants' invention as claimed is patentable over a combination of Morella et al., taken in view of Howard et al. and Bogardus et al. Morella et al. and Howard et al. disclose hundreds, if not thousands, of possible drugs, none of which includes 2′,3′-dideoxyinosine. In fact, ddI would not be included in the Morella et al. teachings since it is not a drug of low water-solubility. Furthermore, Morella et al. and Howard et al. do not disclose or suggest a procedure for making beadlets or pellets containing at least 80% by weight of the core of 2′,3′-dideoxyinosine. Bogardus et al. disclose formulations containing salts of 2′,3′-dideoxyinosine

but does not disclose or suggest beadlets or pellets, or beadlets or pellets containing at least 80% by weight 2',3'-dideoxyinosine (and not a salt thereof). There is nothing in the teachings of Morella et al. and Howard et al. which would suggest to one skilled in the art that the Morella et al. and Howard et al. formulations could include 2',3'-dideoxyinosine. All drug compounding techniques do not apply to all drugs. Bogardus et al. do not give the slightest hint or suggestion as to how to compound 2',3'-dideoxyinosine into a formulation containing at least 80% by weight 2',3'-dideoxyinosine in the core or otherwise. Bogardus et al. do not disclose or how to make beadlets or pellets of high drug concentration as claimed herein. There is nothing in any of the cited references which suggests or gives the slightest hint that 2',3'-dideoxyinosine could be compounded into a beadlet or pellet formulation containing at least 80% by weight 2',3'-dideoxyinosine (and not a salt thereof). Even if the techniques of the cited references were combined, the combination would not disclose or suggest to one skilled in the art how a beadlet containing at least 80% 2',3'-dideoxyinosine would be made. Accordingly, it is submitted that the cited combination of references are no more relevant than each taken alone and do not make Appellants' composition as claimed obvious.

Appellants are not claiming a process or a product by process herein. However, the fact that the cited references do not disclose or suggest a procedure for preparing beadlets or pellets of high concentration of 2',3'-dideoxyinosine as claimed further support Appellants' case for patentability of their beadlet containing at least 80% by weight 2',3'-dideoxyinosine.

In applying the criteria for patentability as enunciated in Graham v. John Deere Co., supra, it is seen that:

(1) the scope of the content of the prior art has been reviewed above.

(2) the differences between the invention and the prior art have been set out, namely, that the prior art does not disclose or suggest an enteric coated beadlet containing at least 80% by weight ddI.

(3) the level of ordinary skill in the art is exceedingly high and involves scientists having Masters, Ph.D. and M.D. degrees.

It is submitted that there is no disclosure or suggestion in any of the cited references or combination thereof of the claimed composition. Accordingly, absent the use of hindsight in view of Appellants' disclosure, there would be no reason for one skilled in the art reading the cited references to combine these references. The use of hindsight in view of Appellants' disclosure in combining references to reject Appellants' claims is clearly improper in view of In re Pye et al., 148

U.S.P.Q. 426 (CCPA 1966), ACS Hospital Systems, Inc. v. Montefiore Hospital, supra.; and W.L. Gore & Assoc., Inc. v. Garlock, Inc., supra.

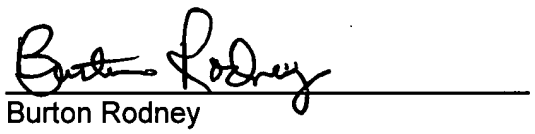
CONCLUSION

The Examiner has not established any factual basis sufficient to support the Examiner's conclusions and thus establish a prima facie case for obviousness of Appellants' invention as claimed. In re Piasecki, 745 F.2d 1468, 223 U.S.P.Q. 785 (Fed. Cir. 1984). In essence, the Examiner has merely alleged that the differences between Appellants' invention and the cited art are obvious, but has not set forth any basis in logic or scientific principle to support such contention as required under In re Soli, 317 F.2d 941, 127 U.S.P.Q. 797 (CCPA 1963). The very combination of references is improper as being based on hindsight in view of Appellants' disclosure.

In view of the fact that Appellants' invention as defined in Claims 5, 7 to 24 and 27 to 31 of this application, is neither disclosed nor suggested in or made obvious by the cited prior art, it is submitted that Appellants have shown that their invention as claimed is not anticipated by and is clearly patentable over the cited combination of references. Therefore, it is believed that the Examiner's final rejection of the claims on appeal should be reversed and that such claims should be allowed.

Appellants hereby waive an oral hearing.

Respectfully submitted,



Burton Rodney
Attorney for Appellants
Reg. No. 22,076

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
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(609) 252-4336

Date: July 14, 2003

CLAIMS ON APPEAL

-- 5. (Amended) A pharmaceutical composition comprising a core in the form of a beadlet and an enteric coating for said core, said core comprising about 80% to about 100% by weight of an acid labile medicament which is 2',3'-dideoxyinosine, about 0% to about 10% by weight of a disintegrant, and about 0% to about 10% by weight of a binder selected from the group consisting of sodium carboxymethylcellulose, hydroxypropylmethylcellulose, potassium alginate, sodium alginate and partially pregelatinized corn starch, said composition being devoid of a protective coat or subcoat between the core and the enteric coating. --

7. The pharmaceutical composition of Claim 5 wherein the weight ratio of enteric coating to core is between about 0.05:1 to about 0.6:1.

8. The pharmaceutical composition of Claim 5 wherein said enteric coating comprises a polymer and a plasticizer.

9. The pharmaceutical composition of Claim 8 wherein said polymer is selected from the group consisting of hydroxypropylmethylcellulose phthalate, polyvinyl acetate phthalate and cellulose acetate phthalate.

10. The pharmaceutical composition of Claim 8 wherein said polymer comprises a methacrylic acid copolymer.

11. The pharmaceutical composition of Claim 10 wherein said enteric coating includes the methacrylic acid copolymer in an amount within the range of from about 5 to about 30% of the total composition weight, and said plasticizer in an amount within the range from about 0.5 to about 6% of the total composition weight.

12. The pharmaceutical composition of Claim 10 wherein .said methacrylic acid copolymer is methacrylic acid copolymer.

13. The pharmaceutical composition of Claim 8 wherein said plasticizer is triethyl citrate, triacetin, tributyl sebecate, or polyethylene glycol.

14. The pharmaceutical composition of Claim 8 wherein said plasticizer is diethyl phthalate.

15. The pharmaceutical composition of Claim 8 wherein said enteric coating includes methacrylic acid copolymer and diethyl phthalate.

16. The pharmaceutical composition of Claim 5, further comprising an anti-adherent coating disposed on the exterior of said enteric coating.

17. The pharmaceutical composition of Claim 16 wherein said anti-adherent coating is a hydrophobic material.

18. The pharmaceutical composition of Claim 17 wherein the anti-adherent coating is magnesium stearate or fumed silica.

19. The pharmaceutical composition of Claim 18 wherein the anti-adherent coating is talc.

20. The pharmaceutical composition of Claim 16 wherein said anti-adherent is present in an amount within the range from about 0.1% to about 4.0% of the total composition weight.

21. The pharmaceutical composition of Claim 5 wherein said disintegrant is cross-linked sodium carboxymethylcellulose, corn starch, or cross linked polyvinlpyrrolidone.

22. The pharmaceutical composition of Claim 5 wherein said disintegrant is sodium starch glycolate.

23. The pharmaceutical composition of Claim 5 wherein said binder is alkaline.

24. The pharmaceutical composition of Claim 23 wherein 5 said binder is sodium carboxymethylcellulose.

-- 27. (Amended) The pharmaceutical composition of Claim 5 wherein said core comprises about 95% by weight 2′,3′-dideoxyinosine, about 1% by weight sodium carboxymethylcellulose and about 4% by weight sodium starch glycolate. --

-- 28. (Amended) The pharmaceutical composition of Claim 5 wherein said composition is encapsulated in a capsule for oral administration. --

29. The pharmaceutical composition of Claim 28 wherein said capsule is filled with said composition in an amount equivalent to attain a dosage of ddI required for twice daily administration.

30. The pharmaceutical composition of Claim 28 wherein said capsule is filled with said composition in an amount equivalent to attain a dosage of ddI required for once daily administration.

31. A pharmaceutical composition comprising:

a) a dissolvable capsule; and

b) the pharmaceutical composition of Claims 5, 16, or 27 which is encapsulated within said dissolvable capsule.

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MARCH 17, 1999

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BRISTOL-MYERS SQUIBB COMPANY
BARRY J. MARENBERG, ESQ.
P.O. BOX 4000
PRINCETON, NEW JERSEY 08543-4000

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NUMBER OF PAGES: 3

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
ULLAH, ISMAT

DOC DATE: 07/13/1998

ASSIGNOR:
WILEY, GARY J.

DOC DATE: 07/13/1998

ASSIGNEE:
BRISTOL-MYERS SQUIBB COMPANY
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SERIAL NUMBER: 09118418
PATENT NUMBER:

FILING DATE: 07/17/1998
ISSUE DATE:

JOANN STEWART, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

Docket Number TN2

Please return to: Burton Rodney
Patent Department
Bristol-Myers Squibb Company
Post Office Box 4000
Princeton, New Jersey 08543-4000

ASSIGNMENT

Pursuant to contractual obligations heretofore assumed by me and/or for other good and valuable consideration, receipt of which is hereby acknowledged, we,

Ismat Ullah	Gary J. Wiley
2 Mockingbird Court	72 Tuscany Drive
Cranbury, N.J. 08512	Jackson, N.J. 08527

having made a certain invention for which a United States patent application entitled **ENTERIC COATED PHARMACEUTICAL TABLET AND METHOD OF MANUFACTURING** has been prepared, do hereby assign to Bristol-Myers Squibb Company, a Delaware corporation, having a place of business at Lawrenceville-Princeton Road, Princeton, New Jersey 08543-4000, its successors and assigns, the entire right, title, and interest in and to said improvements, said provisional application, any application claiming priority from said provisional application, filed in any country, and any patents to be granted thereon, and all divisions, continuations, reissues, and extensions thereof in all countries; and we hereby authorize and request the Commissioner of Patents and Trademarks to issue any such United States patent to Bristol-Myers Squibb Company, its successors and assigns, and we agree to communicate to Bristol-Myers Squibb Company or its representatives any facts known to us respecting said improvements, to testify in any legal proceedings, sign all lawful papers, execute all divisional, continuing, and reissue applications, make all rightful declarations and oaths, and in general to do everything possible to aid Bristol-Myers Squibb Company, its successors, assigns and nominees to obtain and enforce proper protection for said improvements in all countries.

IN WITNESS WHEREOF, we have hereto set our hands and seals

Ismat Ullah

STATE OF New Jersey)
) ss.
COUNTY OF Middlesex)

On the 13 day of July, 1998, before me came Ismat Ullah, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Kathleen McElarney
Notary Public

[SEAL]

Continued on page 2

KATHLEEN MC ELARNEY
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires Mar. 21, 2002

IN WITNESS WHEREOF, we have hereto set our hands and seals

Gary J. Wiley

STATE OF New Jersey)
) ss.
COUNTY OF Middlesex)

On the 13 day of July , 1998, before me came Gary J. Wiley, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he executed it.

Kathleen McElarney
Notary Public

[SEAL]

KATHLEEN MC ELARNEY
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires Mar. 21, 2002